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# Potentiation of Hepatic and Renal Toxicity of Various Compounds by Prior Exposure to Polybrominated Biphenyls

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**Mice ingesting a standard rodent diet supplemented with polybrominated biphenyls (PBBs) were more susceptible to chlorinated hydrocarbon solvent-induced renal and hepatic damage, as well as the lethal effects of $CHCl_3$ and $CCl_4$, than were mice consuming control diet. As little as 0.025 ml/kg $CHCl_3$ caused a significant increase in serum glutamic oxaloacetic transaminase (SGOT) and blood urea nitrogen (BUN) and a significant decrease in renal cortical slices accumulation of *p*-aminohippurate (PAH) in PBB-pretreated but not control mice. SGOT and serum glutamic pyruvate transaminase (SGPT) were greater in PBB-pretreated mice than in control mice after 0.125 and 0.005 ml/kg $CCl_4$, respectively. Renal cortical PAH accumulation was greatly reduced in PBB-pretreated but not control mice after 0.125 ml/kg $CCl_4$. The solvent-induced decrease in PAH accumulation was also greater in PBB-pretreated mice than in control mice following administration of 1.0 ml/kg trichloroethylene (TRI) and 0.15 ml/kg 1,1,2-trichloroethane (TCE).**

## Introduction

Much effort has been expended in studying the toxicology of halogenated aromatic hydrocarbons. Characteristically, these compounds are persistent environmental pollutants which can become contaminants of foodstuffs and be ingested by humans or domestic animals through the diet. Once ingested, such chemicals have long tissue half-lives because of their highly lipophilic nature. One such class of chemicals, the polybrominated biphenyls (PBBs), were developed as fire retardants but were accidentally mixed into animal feed resulting in heavy exposure of domestic farm animals to dietary PBBs. Secondary exposure of humans to PBBs occurred from ingestion of meat and dairy products derived from contaminated livestock (*1*). As can be seen from the other studies presented at this conference, several abnormalities have been induced by exposure of animals to high doses of PBBs. The toxicological significance of chronic, low-level, dietary PBB exposure, though, has not been thoroughly evaluated.

One of the most striking features of PBB exposure is the resultant hepatic hypertrophy and greatly increased activities of microsomal mixed function oxygenases (MFO) (*2*). Increased MFO activities after PBB administration can be demonstrated in the kidney as well as the liver (*3*). Though commonly regarded as the functional mediators of xenobiotic metabolism, MFOs can be instrumental in toxification as well as detoxification processes (*4, 5*). For example, it has been proposed that many of the small, aliphatic, halogenated hydrocarbon solvents are dependent upon biotransformation for manifestation of hepatic and renal injury. Studies involving use of *in vitro* activation techniques have suggested that microsomal enzymes are necessary for generation of the toxic metabolites of solvents such as chloroform ($CHCl_3$) (*6*), carbon tetrachloride ($CCl_4$) (*7*), trichloroethylene (*8*), and 1,1,2-trichloroethane (TCE) (*9*). Thus, it was of interest to determine the effects of PBB-induced stimulation of microsomal enzymes on the toxicity of several chlorinated aliphatic hydrocarbon solvents.

## Methods

Adult, male, ICR mice (20-30 g) were housed in groups of six in clear plastic shoe-box type cages in a well-ventilated, light-cycle controlled room

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maintained at 22±1°C and allowed food and water *ad libitum*.

### Treatments

Polybrominated biphenyls (PBBs as FireMaster BP-6) were dissolved in acetone and mixed slowly and evenly into finely ground Wayne Lablox to produce final concentrations of 0, 1, 20, 25, or 100 ppm PBB. The mice were maintained on control (0 ppm PBB) or PBB-supplemented diets for 14-28 days before a single IP injection of one of several doses of chloroform ($CHCl_3$), carbon tetrachloride ($CCl_4$), trichloroethylene (TRI) or 1,1,2-trichloroethane (TCE). All solvents were dissolved in corn oil and injected in a total volume of 5 ml/kg. The mice were sacrificed 24 hr ($CHCl_3$, TRI, TCE) or 48 hr ($CCl_4$) after solvent injection by decapitation. Blood was collected in disposable glass tubes. Livers and kidneys were quickly but carefully excised, cleaned of extraneous tissue, and weighed. Thin slices of renal cortex were cut free-hand.

### Serum Assays

Whole blood was allowed to clot for 1-2 hr and carefully centrifuged. Serum was drawn off and refrigerated till the time of assay. Blood urea nitrogen (BUN) was determined by use of Sigma reagents (Sigma Chemical Co., St. Louis, Mo.) and serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) by the method of Reitman and Frankel (*10*).

### PAH *S/M* Ratio

Thin renal cortical slices were incubated in a phosphate-buffered medium (*11*) containing $2.5 \times 10^{-5}M$ *p*-aminohippurate (PAH) and $1 \times 10^{-2}M$ acetate for 90 min at 25°C under an atmosphere of 100% $O_2$. Slices were then blotted, weighed, and homogenized in 10% trichloroacetic acid. An aliquot of medium was treated in the same manner. The precipitated protein was pelleted by centrifugation and samples of the supernatant fraction acidified with 0.25 volumes of 1*N* HCl and placed in a boiling water bath for 1 hr to hydrolyze any acetylated PAH. PAH was determined by the method of Smith et al. (*12*). Accumulation of PAH was represented as the slice-to-medium ratio (*S/M*) where *S* is in units of mg PAH/g tissue and *M* is mg PAH/ml medium. The percent decrease in PAH accumulation was determined by using the formula (*13*):

$$\%\,\text{Decrease} = \frac{(\text{Control}\,S/M) - (\text{Treated}\,S/M)}{(\text{Control}\,S/M) - 1}$$

### $LD_{50}$ Determinations

Mice were maintained on 0 or 100 ppm PBB-supplemented diets for 14 days prior to a single IP injection of various doses of $CHCl_3$, dissolved in corn oil, in a total volume of 5 ml/kg. Another group of mice were maintained on 0, 20, or 100 ppm PBB-supplemented diets for 20 days prior to a single IP injection of various doses of $CCl_4$, dissolved in corn oil, in a total volume of 5 ml/kg. The number of deaths occurring within 24, 48, 96, and 168 hr were recorded. The $LD_{50}$ was calculated according to the methods of Litchfield and Wilcoxin (*14*).

### Statistics

Data were analyzed by analysis of variance, randomized complete block design, and treatment means compared using the least significant difference (LSD) test (*15*) with $p < 0.05$ as the criterion of significance.

## Results

The liver weight-to-body weight ratio (LW/BW) was increased in mice consuming dietary PBBs (Tables 1–4) The increase in LW/BW was proportional to the concentration of PBB in the diet (Table 1) and to the duration of PBB feeding. The LW/BW after 14 days on 100 ppm PBBs was 162% of control (Table 1) and 230% of control after 28 days on 100 ppm PBBs (Table 3). Since weight differences between control and treated mice were not significant (data not shown), it would appear that increased LW/BW was due to liver hypertrophy. No elevation of serum glutamic oxaloacetic transaminase (SGOT) was evident in control mice following doses of $CHCl_3$ of up to 50 μl/kg, suggesting that these were subhepatotoxic doses of $CHCl_3$ in normal mice (Table 1). Mice ingesting 100 ppm PBBs exhibited a slight rise in SGOT. As the dose of $CHCl_3$ was increased, however, SGOT continued to rise suggesting that these doses of $CHCl_3$ (25 and 50 μl/kg) were toxic to the liver in mice consuming 100 ppm PBBs (Table 1).

The kidney weight-to-body weight ratio (KW/BW) was not affected by dietary PBBs nor by $CHCl_3$ administration in doses up to 50 μl/kg in mice consuming 0 ppm PBB (Table 2). Mice ingesting PBB-supplemented diets, however, responded to 50 μl/kg $CHCl_3$ with increased KW/BW (Table 2). Since body weights were not affected by dietary PBB, it appeared that PBB enhanced the renal toxicity of $CHCl_3$.

Blood urea nitrogen concentrations (BUN) were similarly unaffected by dietary PBB or $CHCl_3$ ad-

**Table 1. Effect of PBB and $CHCl_3$ on mouse liver weight-to-body weight ratio (LW/BW) and serum glutamic oxaloacetic transaminase activity (SGOT).[a]**

| Parameter | PBB, ppm | $CHCl_3$ μl/kg 0 | 2.5 | 5.0 | 25.0 | 50.0 |
|---|---|---|---|---|---|---|
| LW/BW × 100 | 0 | 5.97 ± 0.23 | 5.93 ± 0.30 | 6.47 ± 0.40 | 6.09 ± 0.19 | 6.39 ± 0.13 |
| | 1 | 6.10 ± 0.19 | 6.17 ± 0.10 | 6.11 ± 0.13 | 5.61 ± 0.15 | 6.01 ± 0.17 |
| | 25 | 6.91 ± 0.31[b] | 7.36 ± 0.19[b] | 6.76 ± 0.12 | 7.35 ± 0.12[b] | 6.46 ± 0.12 |
| | 100 | 9.68 ± 0.38[b] | 9.74 ± 0.30[b] | 9.64 ± 0.25[b] | 10.14 ± 0.34[b] | 9.54 ± 0.23[b] |
| SGOT, U/ml | 0 | 242 ± 40 | 250 ± 62 | 311 ± 48 | 226 ± 27 | 267 ± 81 |
| | 1 | 285 ± 63 | 322 ± 41 | 334 ± 23 | 403 ± 62 | 412 ± 94 |
| | 25 | 173 ± 21 | 148 ± 46 | 196 ± 39 | 232 ± 27 | 308 ± 61 |
| | 100 | 385 ± 27[b] | 512 ± 39[b] | 529 ± 92[b] | 1274 ± 283[b,c] | 1340 ± 306[b,c] |

[a] Mice were maintained on 0, 1, 25, or 100 ppm PBB-supplemented diets for 14 days prior to a single IP injection of 0, 2.5, 5.0, 25.0, or 50.0 μl/kg $CHCl_3$. LW/BW and SGOT were determined 24 hr after administration of $CHCl_3$. Data are represented as means ± 1 standard error of six animals.

[b] Significant increase in comparison to mice receiving the same dose of $CHCl_3$ but ingesting 0 ppm PBB.

[c] Significant increase in comparison to mice ingesting the same dietary concentration of PBB but receiving 0.0 μl/kg $CHCl_3$.

**Table 2. Effect of PBB and $CHCl_3$ on mouse kidney weight-to-body weight ratio (KW/BW), blood urea nitrogen (BUN) concentration, and *p*-aminohippurate accumulation (PAH *S/M*).[a]**

| Parameter | PBB, ppm | $CHCl_3$, μl/kg 0 | 2.5 | 5.0 | 25.0 | 50.0 |
|---|---|---|---|---|---|---|
| KW/BW × 100 | 0 | 1.54 ± 0.05 | 1.64 ± 0.08 | 1.68 ± 0.05 | 1.63 ± 0.08 | 1.70 ± 0.10 |
| | 1 | 1.49 ± 0.04 | 1.54 ± 0.04 | 1.47 ± 0.04 | 1.46 ± 0.08 | 1.98 ± 0.07[b,c] |
| | 25 | 1.47 ± 0.03 | 1.55 ± 0.03 | 1.46 ± 0.05 | 1.76 ± 0.03 | 2.12 ± 0.04[b,c] |
| | 100 | 1.58 ± 0.04 | 1.37 ± 0.04 | 1.42 ± 0.06 | 1.70 ± 0.19 | 2.21 ± 0.09[b,c] |
| BUN, mg% | 0 | 21 ± 1.3 | 23 ± 1.6 | 27 ± 3.7 | 26 ± 2.6 | 28 ± 3.1 |
| | 1 | 22 ± 3.6 | 21 ± 2.2 | 23 ± 4.1 | 35 ± 3.8 | 43 ± 3.6 |
| | 25 | 22 ± 2.0 | 24 ± 1.8 | 21 ± 2.0 | 47 ± 4.9[b,c] | 84 ± 6.2[b,c] |
| | 100 | 21 ± 1.8 | 22 ± 2.6 | 28 ± 2.0 | 81 ± 9.3[b,c] | 108 ± 10.1[b,c] |
| Decrease in PAH *S/M*, % | 0 | — | 1.8 ± 0.9 | 2.7 ± 3.6 | 22.1 ± 13.3 | 63.8 ± 18.2 |
| | 1 | 0.4 ± 0.3 | 2.9 ± 1.2 | 22.6 ± 11.2 | 53.6 ± 14.2[b,c] | 58.5 ± 16.2[b,c] |
| | 25 | 0.0 | 3.6 ± 1.7 | 30.1 ± 19.3 | 42.8 ± 18.2[b,c] | 78.1 ± 23.7[b,c] |
| | 100 | 0.0 | 34.6 ± 7.8[b] | 35.0 ± 10.9[b,c] | 49.3 ± 17.5[b,c] | 38.2 ± 14.6[b,c] |

[a] Mice were maintained on 0, 1, 25, or 100 ppm PBB-supplemented diets for 14 days prior to a single IP injection of 0, 2.5, 5.0, 25.0, or 50.0 μl/kg $CHCl_3$. KW/BW, BUN, and PAH *S/M* were determined 24 hr after administration of $CHCl_3$. Data are represented as means ± 1 standard error of six animals.

[b] Significant increase in comparison to mice receiving the same dose of $CHCl_3$ but ingesting 0 ppm PBBs.

[c] Significant increase in comparison to mice ingesting the same dietary concentration of PBBs but receiving 0.0 μl/kg $CHCl_3$.

ministration in control mice (Table 2). Significant increases were evident, though, in mice ingesting 25 or 100 ppm PBB after 25 or 50 μl/kg $CHCl_3$ (Table 2).

A significant depression in accumulation of the organic anion *p*-aminohippurate (PAH) by renal cortical slices from control mice was evident only after administration of 50 μl/kg $CHCl_3$ (Table 2). Significant depressions were evident after 25 μl/kg $CHCl_3$ in mice consuming 1 or 25 ppm PBB, and after as little as 2.5 μl/kg $CHCl_3$ in mice consuming 100 ppm PBB (Table 2).

LW/BW was increased in control mice 48 hr after injection of 0.125 and 0.625 ml/kg $CCl_4$ (Table 3), indicating hepatic damage at these doses. Similar increases were not evident in mice on 100 ppm PBB though livers were already more than double normal size (Table 3).

SGOT and serum glutamic pyruvic transaminase (SGPT) were elevated by 0.125 and 0.625 ml/kg $CCl_4$ in control mice (Table 3). A significant rise in SGOT was evident also in mice ingesting 100 ppm PBB following administration of 0.125 ml/kg $CCl_4$. The increase in the PBB-pretreated mice was greater than the increase in control mice. SGPT was elevated slightly by PBB ingestion (Table 3). A significant increase in SGPT was evident after 0.005 ml/kg $CCl_4$ in comparison to vehicle in mice ingesting 100 ppm PBB (Table 3) suggesting that PBB-pretreatment "sensitized" mice to the relative

Table 3. Effect of PBB and $CCl_4$ on liver and kidney weight-to-body weight ratios (LW/BW, KW/BW), serum glutamic oxaloacetic and pyruvic transaminases (SGOT, SGPT), blood urea nitrogen (BUN), and *p*-aminohippurate accumulation (PAH *S/M*).[a]

| Parameter | PBB, ppm | $CCl_4$, ml/kg 0.0 | 0.005 | 0.025 | 0.125 | 0.625 |
|---|---|---|---|---|---|---|
| LW/BW × 100 | 0 | 5.93 ± 0.10 | 5.74 ± 0.17 | 5.77 ± 0.10 | 6.54 ± 0.20[b] | 7.51 ± 0.10[b] |
| | 100 | 13.62 ± 0.35[c] | 13.10 ± 0.95[c] | 13.10 ± 0.50[c] | 13.13 ± 0.40[c] | Expired |
| SGOT, U/ml | 0 | 56.3 ± 7.6 | 41.3 ± 4.9 | 65.0 ± 4.9 | 147.5 ± 23.3[b] | 301.2 ± 50.2[b] |
| | 100 | 54.5 ± 7.7 | 57.8 ± 6.2 | 70.7 ± 9.8 | 384.5 ± 36.2[b,c] | Expired |
| SGPT, U/ml | 0 | 26.8 ± 3.0 | 24.0 ± 3.4 | 29.2 ± 4.1 | 133.8 ± 6.8[b] | 205.2 ± 12.0[b] |
| | 100 | 45.0 ± 5.7[c] | 93.0 ± 17.8[b,c] | 126.7 ± 23.1[b,c] | 199.7 ± 16.6[b,c] | Expired |
| KW/BW × 100 | 0 | 1.51 ± 0.03 | 1.49 ± 0.03 | 1.60 ± 0.01 | 1.46 ± 0.01 | 1.95 ± 0.20[b] |
| | 100 | 1.42 ± 0.02 | 1.45 ± 0.04 | 1.45 ± 0.03 | 1.46 ± 0.04 | Expired |
| BUN, mg% | 0 | 11.4 ± 1.8 | 12.0 ± 1.3 | 11.8 ± 1.2 | 10.6 ± 1.2 | 20.2 ± 1.8 |
| | 100 | 13.5 ± 1.7 | 14.0 ± 1.4 | 14.3 ± 1.7 | 18.5 ± 1.6 | Expired |
| Decrease | 0 | — | — | 0.1 ± 0.2 | 2.9 ± 1.8 | 31.2 ± 19.7 |
| in PAH *S/M*, % | 100 | 0.6 ± 0.3 | 3.7 ± 2.6 | 13.1 ± 8.2 | 74.0 ± 26.8[b,c] | Expired |

[a] Mice were maintained on diet supplemented with 0 or 100 ppm PBB for 28 days prior to a single IP injection of 0.000, 0.005, 0.025, 0.125, or 0.625 ml/kg $CCl_4$. All parameters were measured 48 hr after administration of $CCl_4$. Data are represented as means ± 1 standard error of six animals.

[b] Significant increase in comparison to mice ingesting the same dietary concentration of PBB but receiving 0.000 ml/kg $CCl_4$.

[c] Significant increase in comparison to mice receiving the same dose of $CCl_4$ but ingesting 0 ppm PBB.

Table 4. Effect of PBB, TRI, and TCE on mouse liver and kidney weight-to-body weight ratios (LW/BW, KW/BW), serum glutamic oxaloacetic and pyruvic transaminases (SGOT, SGPT) blood urea nitrogen (BUN) and *p*-aminohippurate accumulation (PAH *S/M*).[a]

| Parameter | PBB, ppm | Control 0.0 | TRI, 0.5 ml/kg | TRI, 1.0 ml/kg | TCE, 0.15 ml/kg |
|---|---|---|---|---|---|
| LW/BW × 100 | 0 | 6.16 ± 0.04 | 5.80 ± 0.22 | 5.71 ± 0.10 | 6.49 ± 0.20 |
| | 100 | 9.61 ± 0.05[b] | 9.53 ± 0.14[b] | 9.42 ± 0.28[b] | 9.52 ± 0.45[b] |
| SGOT, U/ml | 0 | 37.2 ± 4.1 | 50.8 ± 3.6 | 55.3 ± 6.6 | 40.7 ± 2.8 |
| | 100 | 42.7 ± 3.8 | 44.3 ± 2.4 | 62.3 ± 9.2 | 50.2 ± 3.7 |
| KW/BW × 100 | 0 | 1.55 ± 0.04 | 1.64 ± 0.03 | 1.56 ± 0.04 | 1.54 ± 0.05 |
| | 100 | 1.53 ± 0.02 | 1.63 ± 0.03 | 1.52 ± 0.05 | 1.51 ± 0.04 |
| BUN, mg% | 0 | 15.6 ± 1.8 | 17.4 ± 1.4 | 18.6 ± 1.4 | 15.1 ± 1.3 |
| | 100 | 16.5 ± 1.3 | 16.5 ± 1.0 | 19.1 ± 2.3 | 14.8 ± 1.4 |
| Decrease | 0 | — | 20.0 ± 4.1[c] | 24.7 ± 2.2[c] | 22.3 ± 2.6[c] |
| in PAH *S/M*, % | 100 | 0.0 | 26.3 ± 2.6[c] | 44.0 ± 6.3[b,c] | 39.2 ± 4.3[b,c] |

[a] Mice were maintained on diet supplemented with 0 or 100 ppm PBB for 14 days prior to a single IP injection of vehicle (0.0), 0.5 or 1.0 ml/kg trichloroethylene (TRI), or 0.15 ml/kg 1,1,2-trichloroethane (TCE). All parameters were measured 24 hr after administration of TRI or TCE. Data are represented as means ± 1 standard error of six determinations.

[b] Significant increase in comparison to mice receiving the same dose of solvent but ingesting 0 ppm PBB.

[c] Significant increase in comparison to mice ingesting the same dietary concentration of PBB but receiving only vehicle.

hepatotoxic effects of $CCl_4$. $CCl_4$ at a level of 0.625 ml/kg produced death in all PBB-pretreated mice but was not lethal to any of the control mice (Table 3).

KW/BW was elevated 48 hr after 0.625 ml/kg $CCl_4$ in control mice (Table 3). This dose was lethal to PBB-pretreated mice. Lower doses were without effect on KW/BW.

BUN concentrations were not elevated by $CCl_4$ administration in mice consuming 0 or 100 ppm PBB (Table 3). Though the PAH *S/M* was reduced by more than 30% following administration of 0.625 ml/kg $CCl_4$ to control mice (Table 3), the depression was not statistically significant. A significant depression was observed, though, following 0.125 ml/kg $CCl_4$ in mice ingesting 100 ppm PBB (Table 3), suggesting that the renal toxicity of $CCl_4$ was enhanced by pretreatment with PBB.

LW/BW was not elevated by administration of trichloroethylene (TRI) or 1,1,2-trichloroethane (TCE) in control mice (Table 4). While dietary PBB caused elevation of LW/BW, no effects of TCE or TRI on LW/BW were evident. SGOT was not elevated by either of these two solvents in mice con-

suming control (0 ppm) or 100 ppm PBB diets (Table 4). Administration of 2.0 ml/kg TRI and 0.3 ml/kg TCE proved to be lethal to mice (data not shown), apparently due to severe depression of the central nervous system.

Neither KW/BW nor BUN were affected by administration of TRI or TCE in mice ingesting 0 or 100 ppm PBB (Table 4).

PAH *S/M* ratios were significantly decreased by administration of TRI and TCE (Table 4). Statistically greater decreases, however, were evident in tissues from mice maintained on 100 ppm PBB after administration of 1.0 ml/kg TRI and 0.5 ml/kg TCE (Table 4). These results suggest enhanced renal toxicity of TRI and TCE in mice pretreated with PBB.

The $LD_{50}$ values of $CHCl_3$ and $CCl_4$ were less in mice maintained on PBB-supplemented diets than in control mice (Table 5). Furthermore, the $CCl_4$ $LD_{50}$ was inversely proportional to the dietary concentration of PBB. Thus, the lethality of $CHCl_3$ and $CCl_4$, as well as the renal and hepatic toxicities, was enhanced by dietary PBB.

**Table 5. Effect of PBB on acute $CHCl_3$ and $CCl_4$ $LD_{50}$.[a]**

| Solvent | PBB, ppm | 96-hr $LD_{50}$, ml/kg[b] | Potency ratio PR[b,c] |
|---|---|---|---|
| $CHCl_3$ | 0 | 1.00 (0.87–1.14) | |
| $CHCl_3$ | 100 | 0.39 (0.35–0.43) | 2.56 (2.11–3.05)[d] |
| $CCl_4$ | 0 | 1.84 (1.55–2.18) | |
| $CCl_4$ | 20 | 1.00 (0.82–1.22) | 1.84 (1.46–2.32)[d] |
| $CCl_4$ | 100 | 0.28 (0.25–0.31) | 6.57 (5.48–7.88)[d] |

[a] Mice were fed diets supplemented with 0, 20, or 100 ppm PBB for 14 ($CHCl_3$) or 20 ($CCl_4$) days prior to a single IP injection of $CHCl_3$ or $CCl_4$, in corn oil, in a total volume of 5 ml/kg. Deaths occurring within 96 hr after solvent administration were recorded and $LD_{50}$ values determined by the method of Litchfield and Wilcoxin (*14*).

[b] The 95% confidence limits are in parentheses following $LD_{50}$ and PR values.

[c] Potency ratio (PR) is defined as the $LD_{50}$ in mice ingesting 0 ppm PBB divided by the $LD_{50}$ in mice ingesting 20 or 100 ppm PBB.

[d] Significant increase in lethality (PR) at $p < 0.05$.

## Discussion

Results presented in this study document that animals ingesting PBB by the dietary route are much more susceptible to the renal and hepatic toxicities of chlorinated hydrocarbon solvents as well as the lethal effects of $CHCl_3$ and $CCl_4$ than are mice consuming control diet. Though not examined in this study other toxic effects of solvent administration may be similarly enhanced by dietary PBBs.

Since PBB administration stimulates microsomal enzyme systems in the liver (*2*) and the kidney (*3*) (which appear to be necessary for the generation of toxic metabolites from aliphatic chlorinated hydrocarbon solvents), it can be assumed that the mechanism of PBB-induced potentiation of solvent toxicity is stimulation of a particular enzyme or enzyme pathway resulting in greater amounts of toxic metabolite being generated in PBB-pretreated mice than in control mice from the same dose of solvent. Thus, the mice ingesting PBBs transformed a greater percentage of the administered dose of solvent to a toxic product than did control mice. Since renal and hepatic lesions are evident in humans as well as other animal species following intoxication with chlorinated hydrocarbon solvents (*16*), it can be expected that PBB ingestion would similarly "sensitize" humans and other animal species to solvent-induced toxicity. Furthermore, there are several chemicals, including many carcinogens, whose toxicity is dependent upon biotransformation of the relatively innocuous parent compound to a toxicant before toxic manifestations become evident. Being a potent but nonspecific inducer of the enzymatic systems which may toxify such compounds, PBBs could increase the hazard of exposure of humans and other animal species to a variety of chemicals transformed to toxicants by the victim's tissues. For example, safe chemical exposure levels for industrial workers are determined in normal subjects, the worker ingesting PBBs may show signs of toxicity even though the amount of toxic chemical to which he is exposed is considered to be within "safe" limits. Furthermore, it has been estimated that 90% of human cancers are chemical in origin (*17*) and that most chemical carcinogens must be "activated" to the ultimate cancer-causing moiety by *in vivo* metabolism (*18*). Thus, long-term exposure to low concentrations of PBB may, by stimulation of microsomal enzyme systems responsible for toxification, "sensitize" victims to the toxic effects of chemicals biotransformed to ultimate toxicants.

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